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INFO-0186

A REVIEW OF THE SCIENTIFIC BASIS FOR THE QUALITY FACTOR FOR NEUTRONS

by

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A research report prepared for the
Atomic Energy Control Board
Ottawa, Canada

April 1986

Canada

Research report

A REVIEW OF THE SCIENTIFIC BASIS FOR THE QUALITY FACTOR FOR FAST NEUTRONS

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ABSTRACT

Recently, the ICRP has recommended* that the quality factor for fast neutrons be increased by a factor of two. They did not give a detailed explanation of the reasons for their recommendations, but indicated that the reasons would be developed as part of a much larger review of the quality factor for all radiations. Since it is AECB's policy to follow ICRP's recommendations unless there is good reason not to do so, and since the changing of the quality factor for neutrons has not been generally accepted by other countries** a review of the scientific basis for the neutron quality factor was requested. This report gives results of that review.

The report reviews the available published information on the relative biological effectiveness (RBE) of neutrons and on the physical basis for the neutron quality factor for use in personnel dosimetry programs. It is concluded that some, but by no means all, of the RBE data supports an increased quality factor, but the relevance of this data to the quality factor for use in radiation protection is not clear for two reasons. Firstly, the biological endpoints are not all directly extrapolatable to late stochastic effects in humans, and secondly, the current conservative selection of a quality factor for neutrons, and the conservative practise of equating whole body dose to the maximum dose equivalent, leads to a factor of about 10 conservatism in the assignment of neutron dose equivalents.

The overall conclusion of the review is that there is no compelling reason to increase the quality factor for neutrons at least until the ICRP has completed its comprehensive review of the subject.

* Statement from the ICRP Paris Meeting of the ICRP. Annals of the ICRP, Vol. 15, No. 3 (1985).

** H.J. Dunster, International News: Commission of the European Communities. Radiological Protection Bulletin (NRPB), No. 67, 14 (1985).

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This work was produced by D.K. Myers and J.R. Johnson under contract to the Atomic Energy Control Board.

RÉSUMÉ

La Commission internationale de protection radiologique (CIPR) a recommandé* récemment que le facteur de qualité des neutrons rapides soit multiplié par 2. Elle n'a pas donné d'explications détaillées des raisons qui l'ont menée à formuler une telle recommandation, mais elle a indiqué qu'elle développerait son point de vue dans le cadre d'un examen plus approfondi des facteurs de qualité pour tous les types de rayonnements. Comme la CCEA a pour politique de suivre les recommandations de la CIPR à moins de bonnes raisons contraires et comme la modification du facteur de qualité des neutrons rapides n'a pas encore été généralement acceptée par d'autres États**, la CCEA a demandé un examen des données scientifiques à partir desquelles on a fixé le facteur de qualité des neutrons.

Le présent rapport examine les renseignements publiés disponibles sur l'efficacité biologique relative (EBR) des neutrons et sur la base physique pour fixer le facteur de qualité des neutrons à utiliser dans les programmes de dosimétrie des travailleurs. Le rapport constate que quelques données seulement sur l'EBR, et non pas toutes, loin de là, appuient l'augmentation du facteur de qualité, mais la pertinence de ces données par rapport au facteur de qualité à utiliser en radioprotection ne ressort pas clairement pour deux raisons. Premièrement, les points limites biologiques ne sont pas tous directement extrapolables jusqu'aux effets stochastiques tardifs chez les humains et, deuxièmement, le choix prudent actuel d'un facteur de qualité des neutrons et la pratique prudente d'égalisation de la dose au corps entier à l'équivalent de dose maximal, donnent un facteur de prudence d'à peu près 10 dans l'attribution de l'équivalent de dose des neutrons.

Il ressort en général de l'examen qu'il n'y a aucune raison contraignante pour augmenter le facteur de qualité des neutrons, au moins jusqu'à ce que la CIPR termine son examen approfondi de la question.

* Paris Meeting of the ICRP, Annals of the ICRP, Vo. 15, No. 3, 1985.

** H.J. Dunster, "International News: Commission of the European Communities", in Radiological Protection Bulletin (NRPB), Vol. 67, No. 14, 1985.

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A. INTRODUCTION

It has been common practise for organizations involved in radiation protection to look to ICRP publications for guidance in such matters as setting exposure limits, assigning quality factors to different types of radiations, etc. Thus, although it often takes some years for regulatory bodies such as the AECB to review ICRP publications and to revise their regulations, regulations normally follow ICRP recommendations unless there are adequate reasons not to do so.

In 1985, the ICRP recommended that the quality factor for fast neutrons be increased by a factor of 2. Their statement was [1]

> "The information now available on the relative biological effectiveness (RBE) for neutrons for a variety of cellular effects in vitro, and for life-shortening in the mouse, is being reviewed by the Commission. The implications of this information will be considered as part of a larger review of recommendations to be undertaken by the Commission over the next four years or so. Meanwhile, in the case of neutrons the Commission recommends an increase in Q by a factor of 2. The permitted approximation for Q for fast neutrons thus changes from 10 to 20.
>
> These changes relate only to neutrons, and no other changes in Q are recommended at this time."

This statement has caused considerable discussion amongst people responsible for radiation protection programs involved with exposures to neutrons. The two main questions that arise from the statement are:

1. What is the scientific basis for the recommendation to double the quality factor?

2. How can this revised quality factor be calculated?

This report focuses primarily on the first question. The second question is addressed in Section C, where neutron dosimetry is reviewed, but it is informative to explore it briefly here.

Neutrons, while normally called ionizing radiation, are not themselves ionizing. Like photons, their ionizing characteristics arise from secondary charged particles produced when they interact with matter. These charged particles are assigned a "quality" to account for the observation that different ionizing particles cause different amounts of biological effects for the same energy deposition. It is generally accepted that the reason for these differences is the difference in the microscopic distribution of deposited energy, mainly by ionization (this will be discussed in more detail in Section 3). The quality factor for neutrons then, is that of the secondary charged particles, which could be electrons, protons, or heavier charged particles such as carbon nuclei. Hence, how can the quality factor for neutrons be changed without changing the quality factor of the secondary charged particles.

It can be recognized by the above brief discussion that any change to the neutron quality factor must involve changes to the quality factor of other radiations as well. This, and the uncertainty in the biological base for any change (see Section B), has resulted in organizations such as the CEC [2] recommending that no action be taken on changing the quality factor for neutrons until the ICRP has completed its more comprehensive review.

This review of the scientific basis for the quality factor for neutrons has essentially resulted in the same conclusion.

B. RELATIVE BIOLOGICAL EFFECTIVENESS (RBE) OF FAST NEUTRONS

1. Review of Basic Concepts

The term RBE indicates the ratio of the doses of the reference radiation and of the test radiation required to produce the same biological effect. For radiation protection purposes, absorbed doses of neutrons were originally multiplied by a given RBE value to obtain doses in "equivalent roentgen" or in "rem". The term RBE was later replaced by the term quality factor (Q) in radiation protection [3], in order to avoid confusion with the traditional use of RBE to describe results obtained in one particular laboratory experiment on one particular biological endpoint.

Q is intended to represent a reasonable single value for the RBE of the test radiation (e.g., neutrons) for induction of late, stochastic effects in human populations exposed to radiation at low doses and low doses rates (i.e., less than 500 mSv per year to any single tissue or less than 50 mSv per year to the whole body). The stochastic effects in question are induction of cancer in the irradiated persons, of genetic changes in their offspring, and possibly of certain congenital abnormalities in the developing fetus [4, 5]. The selected value of Q is not intended to be applicable to the lethal effects of high radiation doses at high dose rate [4], in which case RBE values for most types of ionizing radiation tend to approach a value of one.

It was at one time widely believed that relevant data on the RBE of fast neutrons in humans could be derived from studies on the survivors of Hiroshima and Nagasaki [6-9]; RBE values much greater than 10 were derived for the presumed neutron component in the doses received by the bomb survivors in Hiroshima [9]. This concept, which reportedly influenced the 1980 advisory statement by the U.S. NCRP that it might be necessary to reduce the values for maximum permissible neutron doses, has been largely abandoned as a result of recent revisions of the Hiroshima-Nagasaki dosimetry [10]. Consequently the desired estimate of Q for neutrons has to be derived from the results of laboratory experiments on animals and other living organisms, and from microdosimetric interpretations of these results.

Data from many laboratory experiments can be fitted by the general types of dose-response curves illustrated in Figure 1 for induction of late biological effects by high LET radiation (e.g. neutrons) and by low LET radiation (e.g. X-rays). The value of the RBE that is relevant to Q can be defined by the slopes of the initial linear portions of these dose-response curves at low doses and/or low dose rate. There are many problems involved in estimating these initial slopes, due mainly to the fact that reliable data at very low radiation doses cannot be obtained in animal studies. Consequently theoretical interpretations [cf. 11] of the data play an important role in predicting radiation effects at doses and dose-rates which are so low that no effects can be measured in humans or in other animals.

In various experiments with plant systems and with mammalian cells in vitro, the RBE for fast neutrons reaches a maximum for neutrons of about 0.4 to 0.6 MeV [10, 12]. The RBE at 0.4 MeV is roughly 4 times that of 10 MeV neutrons. These results are in broad agreement with predictions based on the theory of dual radiation action [11, 13] and have been taken into consideration in deriving Q values for neutrons of different energies [50].

The reference radiation is traditionally taken to be 200 kVp X-rays [14]. However, most biological experiments on the effects of radiation at low dose rate have utilized ^{60}Co or ^{137}Cs γ-rays rather than X-rays as the source of low LET radiation in RBE studies. Because of this fact, considerable caution is required in interpreting the results of these studies. Although the international committees have assumed that the RBE for γ-rays would not be less than 0.8 when compared to X-rays [4,10,15], this assumption does not agree with the results of some laboratory studies where γ-rays at low dose rate are found to be 2 to 5 times less effective than X-rays. These studies will be described in more detail below.

2. Non-stochastic Effects

Although the value of Q is most critical for evaluation of the stochastic hazards of low levels of radiation, the same value is used to calculate dose equivalents for the non-stochastic effects of high radiation doses. These non-stochastic effects include, for example, skin burns, sterility, fibrosis and cataracts. Non-stochastic effects have been reviewed in detail in a recent UNSCEAR report [10]. The highest RBE values cited were in the region of 20 for induction of lens opacities by low doses of 0.4 MeV neutrons. RBE values for fast neutrons were generally in the region of 1 to 5 for induction of other non-stochastic effects [10].

3. Visible Chromosomal Abnormalities

The study of radiation-induced chromosomal abnormalities which are visible through a microscope has played a major role over several decades in our basic understanding of radiation effects. These abnormalities can be divided into two broad categories: (a) gross abnormalities such as formation

of ring chromosomes, dicentric chromosomes and acentric fragments or micronuclei (i.e., loss of major portions of the genetic information from the cell nucleus) which will usually result in loss of cell reproductive viability and are therefore considered "unstable", and (b) minor abnormalities such as translocations (i.e., transfer of genetic material from one chromosome to another) which may result in viable cells with altered biological properties.

Interest in the latter biological endpoint for purposes of radiation protection stems from three considerations: (a) Translocations are responsible for an appreciable portion of the total genetic hazards of radiation [10]. (b) Translocation of oncogenes (genetic material associated with uncontrolled cell division) is now thought to be one of the mechanisms responsible for induction of cancer [16]. (c) Induction of chromosomal abnormalities can be studied both in vitro and in intact animals with greater precision and at lower radiation doses than can the induction of genetic changes in the offspring of irradiated animals or the induction of cancer in irradiated animals.

Induction of visible translocations in spermatogonia of mice and other mammals has been extensively studied; in general, the data conform to the general features indicated in Figure 3. In mice, high doses of either X- or γ-rays at high dose rate were almost equally effective [17]. The efficiency of X-rays decreased by a factor of about 2 while that of γ-rays decreased by a factor of about 10 as the dose rate was decreased. Thus γ-rays at low dose rate were roughly 5 times less effective than X-rays at low dose rate [10,17]. The RBE of 0.7-2 MeV neutrons for induction of translocations in mouse spermatogonia was found to be in the region of 3-10 as compared to X-rays at low dose rate (or in the region of 20-80 as compared to γ-rays at low dose rate) [7,17] (Table 1). The data, which frequently came from different laboratories, were not precise enough to distinguish between the effectiveness of 0.7 MeV and 2 MeV neutrons although 14.5 MeV neutrons appeared to be somewhat less effective [7] as expected.

Table 1: Induction of visible translocations in mouse spermatogonia by radiations at low dose and low dose rate [7,17]

Radiation	Translocations per cell per Gy	RBE compared to X-rays
^{137}Cs or ^{60}Co γ-rays	$1.4\text{-}2.3 \times 10^{-3}$	0.1 - 0.2
X-rays	$1.0\text{-}1.8 \times 10^{-2}$	1.0
0.7-2 MeV neutrons	$0.5\text{-}1.1 \times 10^{-1}$	3 - 10

More recent data [18] using fractionated weekly dose of fission neutrons and of γ-rays over a period of 60 weeks indicated RBE values of 10-24 for induction of translocations in mouse spermatogonia, of 18-22 for induction of chromosome fragments in sperm and of 7 for induction of chromatid rearrangements in sperm. All RBE values were estimated with reference to ^{60}Co γ-rays only [18].

Extensive information is also available for the induction of unstable chromosomal abnormalities in human white blood cells (Table 2) and in cultured mammalian cells of different kinds (Table 3). Again the data conform to the general model indicated in Figure 1. In human lymphocytes, γ-rays are 2 to 3 times less effective than X-rays at low doses (Table 2). The limiting RBE for fission neutrons compared to X-rays at low doses is in the region of 15 to 19. In cultured mammalian cells, the limiting RBE for 0.5 MeV neutrons as compared to X-rays at low doses appears to be in the region of 7 to 15 (Table 1). The question of the relative effectiveness of X- and γ-rays in these latter studies is not resolved [20-22]. Data on induction of unstable chromosomal abnormalities are considered highly relevant to the shape of dose-response curves for reproductive survival of irradiated mammalian cells.

Because these gross chromosomal abnormalities are unstable and do not lead to viable cell progeny, their relevance to stochastic hazards of radiation is questionable. A recent publication has however attempted to use data on induction of chromosomal abnormalities to predict the relative effectiveness of radiations to cause cancer in human populations [23]. When tested against relevant experimental data, this approach either adequately predicted or overestimated the carcinogenic and mutagenic effects of neutrons in animals.

4. Genetic Effects

It has been possible to study the genetic effects of radiation in lower organisms with far greater precision than any of the other biological effects of radiation. Two general conclusions have emerged: (a) The incidence of radiation-induced changes is in general directly proportional to the total dose and independent of dose rate after exposure to low doses of low LET radiation. In one particular system, a linear dose-response relationship was still observed with X-rays at doses so low that they would be expected to cause less than one ionization per cell (see Section D); it follows logically that the dose-response relationship should therefore be linear down to zero dose [24]. A similar relationship may be reasonably assumed but has not been proven for any other biological endpoints. (b) The shape of the dose-response relationship for higher doses of low LET radiation at high dose rate and the RBE for neutrons varies considerably for different genetic changes scored in different biological systems (Figure 2). For example, induction of gene conversion in yeast appears to be strictly proportional to radiation dose over a wide range of sublethal doses,

Table 2: RBE for induction of unstable chromosomal abnormalities in human lymphocytes by radiations at low dose [19]

Radiation	RBE compared to X-rays	
	Dicentrics	All unstable abnormalities
^{60}Co γ-rays	0.3-0.4	0.4
X-rays (250 kVp)	1.0	1.0
14.7 MeV neutrons	4.	4.5
7.6 MeV neutrons	10.	9.
0.7-0.9 MeV fission neutrons	15.-17.	15.-19.
6.1 MeV α-particles	6.	3.3

Table 3: RBE for induction of dicentric chromosomes in cultured mammalian cells [20,21]

Radiation	RBE compared to X-rays			
	V-79 cells	RUC-2 cells	R-1,M cells	BHK-21 cells
15 MeV neutrons	5.5	7.5	1.9	5.
4 MeV neutrons	8.5	6.9	1.9	—
2 MeV neutrons	—	—	—	12.
0.5 MeV neutrons	15.	11.	7.	—

relatively independent of dose rate, and to exhibit a low RBE for neutrons [25]. Induction of stamen hair mutations in spiderwort (Tradescantia), on the other hand, has both a linear component and a dose-squared component in the dose-response relationship for low LET radiation at high dose rate; the dose-squared component disappears at low dose rates. The RBE for fast neutrons approaches 50 compared to X-rays at low doses or low dose-rates in the Tradescantia system but is less than 2 in the yeast gene conversion system (Table 4). The RBE for induction of back mutations in yeast by 14 MeV neutrons is also low, about 1.3 [25]. The mechanisms involved in induction of genetic changes in yeast and Tradescantia must differ considerably. It is of some interest to note that γ-rays at low dose rate are less effective than X-rays for induction of mutations in Tradescantia (Table 4), as also appears to be true for induction of visible translocations in mouse spermatogonia (Table 1) and of visible chromosomal abnormalities in human white blood cells (Table 2). This is not true for the yeast system (Table 4).

Limited data are available for induction of forward mutations in cultured mammalian cells (Table 5). Again the shape of the dose-response relationship of low LET radiation at high dose rate and the RBE for neutrons differs considerably depending upon the type of mutation, even in the same cells. Methotrexate-resistant mutations tend to increase in direct proportion to the dose of gamma-rays and to have a low neutron RBE [28]. Thioguanine-resistant mutations respond to gamma-rays in much the same manner as described above for somatic mutations in Tradescantia and exhibit a moderately high neutron RBE [28]. X-rays are roughly twice as effective as gamma-rays at low doses for induction of these mutations [29]. Thioguanine-resistant mutations are produced by deletion of a considerable portion of the genetic material in the chromosome. Mutations (e.g. to ouabain resistance) which appear to depend upon minor changes in the genetic code are not readily induced by ionizing radiation. The mechanisms responsible for induction of methotrexate resistance are uncertain but may depend upon gene amplification [28].

Genetic changes in animals cannot be studied with the same degree of precision as those in yeast and Tradescantia but the dose-response relationship (Figure 3) could be fitted to the same general types of curves indicated in Figure 1. The results of these studies have been reviewed many times because of their critical importance for assessment of the genetic hazards of radiation to humans [7,8,10,17,31]. The RBE for induction of mutations in mouse spermatogonia by 0.7-2 MeV neutrons is in the region of 20-23 as compared to ^{60}Co or ^{137}Cs γ-rays at low dose rate (Table 6). Unfortunately there are not sufficient data to provide a reliable estimate of the RBE compared to X-rays at low dose rate. It does appear that γ-rays at high dose rate are almost as effective as X-rays at high dose rate, and it is well established that γ-rays at low dose rate are 3-4 times less effective than X-rays at high dose rate. Fast neutrons appear to be 5-6 times more effective than X-rays at high dose-rate. The critical information for X-rays at low dose rate or highly fractionated exposure [17] is extremely limited but suggests, as a very tentative conclusion, that the RBE for induction of mutations in mouse spermatogonia by 0.7-2 MeV neutrons might be in the region of 10 as compared to X-rays at low dose rate.

Table 4: RBE for induction of TRP gene conversion in yeast [25] and of pink stamen hair mutations [26,27] in Tradescantia by low doses of radiation

Radiation	RBE compared to X-rays	
	Gene conversion in yeast	Pink mutations in Tradescantia
γ-rays	1.0	0.5
X-rays	1.0	1.0
14 MeV neutrons	1.7	10.
2 MeV neutrons	—	15.
0.7 MeV neutrons	—	31.
0.43 MeV neutrons	—	48.
0.22 MeV neutrons	—	26.
0.065 MeV neutrons	—	15.

TABLE 5: RBE for induction of genetic changes in cultured mammalian cells by low doses of radiation

Radiation	RBE compared to gamma-rays		
	Methotrexate resistance in mouse L5178Y cells [28]	Thioguanine resistance in mouse L5178Y cells [28]	Thioguanine resistance in hamster V-79 cells [29]
gamma-rays	1.0	1.0	1.0
X-rays	-	-	2.
6 MeV neutrons	1.3	8.-9.	-

The RBE for induction of various kinds of genetic changes in insects (fruit flies, silkworm) by fast neutrons is usually in the range of 2-3 as compared to X-rays at high dose rate [17,31]. Values observed in plants and other lower organisms cover a much wider range; in most cases, with the exception of the systems noted earlier (Table 3), these data do not improve our understanding of RBE values that might be applicable at low doses or low dose rates in humans or other mammals.

5. Life Shortening

The shortening of average life span after irradiation has acquired increased interest in view of the conclusion that this effect is due primarily to induction of tumors by radiation when cumulative radiation exposures do not exceed a dose of a few Sv [8,10]. Life shortening by low to moderate radiation exposures can thus be taken as a measure of the total risk of induction of fatal cancers in all tisues in the body.

Exposure to γ-rays at low dose rates is on average about 7 times less effective than X- or γ-radiation at high dose rate for induction of life shortening [10]. The dose-response function for chronic γ-exposure appears to be a simple linear, non-threshold relationship, at least up to a dose rate of about 0.2 Gy per day in mice [10]. Chronic exposure to fission neutrons appears on average to be about 8-13 times more effective than chronic exposure to γ-rays for induction of life shortening in mice; however, at higher dose and dose rates the RBE is frequently found to be about 2 [10]. Various analyses of the data have led to the suggestion that the degree of life shortening induced by fast neutrons is proportional to the square root of the dose rate in the case of chronic exposure or to the square root of the dose in the case of single exposures [10]. These analyses led directly to the conclusion that the RBE for fast neutrons is inversely proportional to the square root of the neutron dose (i.e., RBE is proportional to $1/D_n^{0.5}$). This concept agrees with one microdosimetric interpretation of the data [13] and apparently influenced the 1982 statement of the U.K. National Radiological Protection Board which warned that it might be necessary to reduce maximum permissible neutron doses [32].

However, the assumption that RBE is proportional to $1/D_n^{0.5}$ down to very low radiation doses presents some logical difficulties. When average neutron doses to a tissue are reduced below 0.01 Gy, most of the cells in the tissue receive zero dose, a small percentage will be traversed by one ionizing particle, and the proportion which could be traversed by more than one ionizing particle approaches the vanishing point [8,13]. Consequently the number of cells which could be biologically altered in any way might be expected to be directly proportional to neutron dose in the low dose region. If the biological effects of X- or γ-rays are also proportional to dose in the low dose region, as is assumed for radiation protection purposes and is known to be true for the induction of certain genetic changes in lower organisms [30-32], then the RBE for neutrons cannot continue to increase indefinitely but must reach some limiting value at low radiation doses.

Table 6: Limiting RBE values for induction of mutations in mouse spermatogonia and of life shortening in mice by radiations at low dose or low dose rate

Biological endpoint (and reference)	Neutron energy	RBE compared to Co-60 and Cs-137 γ-rays
Mouse spermatogonia:		
Specific locus mutations [17]	0.7 MeV	23
Specific locus mutations [17]	1-2 MeV	20
Dominant visible mutations [17]	0.7 MeV	20
Life shortening in mice:		
$B6CF_1$ males [34]	Fission	16-22
$B6CF_1$ females [34]	Fission	22-29
BALB/c females [34]	Fission	13-18
$B6CF_1$ females [35]	Fission	12-16

There appears to be increasing agreement that there is in fact a limiting value of the RBE for life shortening induced by neutrons at low radiation doses [33-35]. Storer & Mitchell [34] analyzed published data from the Oak Ridge and Argonne laboratories on the shape of the dose-response curves for life shortening induced by single exposures to fission neutrons at doses of 0.025 to 0.2 Gy and by fractionated exposures resulting in cumulative doses up to 0.8 Gy. The response was found to be proportional to $D_n^{0.9}$ to $D_n^{1.0}$, and not to the function $D_n^{0.5}$ which does provide a reasonable description of the dose-response curve at higher neutron doses. The limiting RBE of fission neutrons compared to γ-rays was found to be 18-29 if the response were proportional to $D_n^{0.9}$ and to be 13-22 in the equally likely event that the response were proportional to $D_n^{1.0}$. The range of RBE in both cases was determined by the strain and sex of the mice (Table 5). No consideration was given to RBE values compared to the standard reference radiation, 200 kVp X-rays.

Thompson et al [35] recently published new additional data on life shortening induced by single exposures of female mice to fission neutrons in doses down to 0.01 Gy. They concluded that the assumption of a response proportional to $D_n^{0.5}$ grossly overestimated the life shortening induced by 0.01-0.03 Gy of neutrons and that the data up to 0.1 Gy of neutrons were best fitted by a linear dose-response relationship. The limiting value for the RBE of fission neutrons compared to γ-rays was in the region of 12 to 16 depending upon the method used to analyse the data (Table 6). Again information on the RBE values compared to X-rays at low doses and/or dose rates is lacking.

6. Cell Transformation

Studies of transformation of mammalian cells *in vitro* from a normal to an oncogenic state are relevant to our understanding of the initial stages of cancer development. The mechanisms of transformation are however still imperfectly understood and there are several methodological problems which are still unresolved [36]. For these reasons, direct projection of the results of these in vitro studies to induction of cancer in the whole animal is not encouraged at the present time [36].

The RBE of 0.5 MeV neutrons as compared to X-rays at low doses was reported to be in the range of 12 to 24 for cell transformation in three different mammalian cell lines tested in one laboratory (Table 7). 15 MeV neutrons were 2-3 times less effective than 0.5 MeV neutrons in one of these cell lines. There are however many problems to be resolved in these transformation studies. Fractionation or protraction of the radiation dose has been reported to have diametrically opposite effects on efficiency of induction of cell transformation in experiments from different laboratories, both for low LET radiations and for neutrons [36]. The effects of other agents on cell transformation by radiation in vitro also require further elucidation. For example, in experiments on one particular cell line under a given set of experimental conditions in one laboratory, neutrons at low dose rate appeared paradoxically to be much less effective than neutrons at high dose rate. The dose-response curve at low doses was apparently linear in both cases. The presence of a tumor promoting agent, a phorbol ester, after irradiation was reported to increase the rate of induction of cell transformation by neutrons to the same level per unit dose whether the dose rate was high or low; on the other hand, the presence of an anti-carcinogenic agent ("Antipain") decreased the effectiveness of neutrons at high dose rate to that of neutrons at low dose rate [38]. Until these unusual results of studies on transformation of mammalian cells in vitro are better understood, caution is required in any attempts to draw general conclusions on carcinogenesis from the data [36].

Table 7: RBE for cell killing and for oncogenic transformation of three mammalian cell lines by low doses of radiation [37].

Cell line	Neutron energy	RBE compared to X-rays	
		cell killing	oncogenic transformation
C3H/10T½	15	3	5
	4.2	6	7
	0.5	13	12
NBCH-3	0.5	14	20
WAGR-2	0.5	22	24

7. Induction of Specific Types of Cancer

Most studies on radiation-induced cancer in animals have utilized a specific strain of rodent that was known from previous studies to be particularly susceptible to induction of one particular type of cancer by ionizing radiation. The same strain is not necessarily the most susceptible to induction of the same type of cancer by other carcinogenic agents [39].

For radiation protection purposes, the number of cancers induced by ionizing radiation at low doses and low dose rates is assumed to be directly proportional to accumulated radiation dose. This assumption is substantiated by studies on life shortening induced by radiation (section B.5) and by some theoretical considerations concerning potential mechanisms of cancer induction [40]. A variety of shapes of dose-response curves is however observed when specific types of cancer are studied in specific strains of rodents; two examples are illustrated in Figure 4. Three main types of dose-response curves can be distinguished:

(a) Data such as those on induction of myeloid leukemia in male RF mice (Figure 4) can be fitted to the general model indicated in Figure 1.

(b) Data on induction of certain other tumors, e.g., breast tumors in female Sprague-Dawley (S-D) rats, by X- or γ-rays tend to exhibit a linear dose-response relationship which is not greatly affected by the dose rate [36]; the effects of neutrons in this particular system will be discussed in more detail below.

(c) The dose-response curves for certain other tumors, e.g. ovarian tumors in female RF mice (Figure 4), show a distinct threshold. This may reflect the need to inactivate a large proportion of hormonally-active cells in the ovary before tumors develop [36]. In other systems, for example, induction of bone sarcomas, there may be a practical threshold because the average latency at low radiation doses exceeds the average lifespan [36]. Apparent or real thresholds cannot be excluded for induction of skin cancer in rats and mice [36]. This does not necessarily mean that similar thresholds must exist for induction of the same types of cancer in humans. It is possible that the effects of any single carcinogenic agent such as ionizing radiation may always tend to be directly proportional to dose when the effects of this agent are superimposed upon those of a wide variety of other carcinogenic, co-carcinogenic and promoting agents to which a human population is exposed. Meaningful RBE data can however be derived from animal data only for those types of tumors which fall into the first two classes noted above.

RBE values observed for cancer induction by fast neutrons in various studies are summarized in Table 8. Most of the RBE values reported are in the range of 5 to 30. Values up to 200 have been reported for acceleration of the appearance of breast cancers in female S-D rats by low doses of fast neutrons; much lower values, in the region of 5-25, are observed for the same endpoint in other strains of rats (Table 8). The data on breast cancer

Table 8: Estimates of RBE for induction of cancer in rodents by fast neutrons at low radiation doses or dose rates

Type of cancer	Strain of rodent (and references)	Neutron energy	Reference radiation	RBE
Myeloid leukemia	RF/U_n mice [41]	Fission	γ	2 - 16
Thymic lymphoma	RF/U_n mice [41]	Fission	γ	2 - 3
Benign breast	S-D/Rij rats [42]	0.5 MeV	X	5 - 7
Benign breast	BN/Bi Rij rats [42]	0.5 MeV	X	12
Benign breast	WAG/Rij rats [42]	0.5 MeV	X	13 - 25
Malignant breast	WAG/Rij rats [42]	0.5 MeV	X	10 - 15
Breast	S-D rats [7,43]	0.43 MeV	X or γ	50 - 200
Breast	ACI rats [44]	0.43 MeV	X	10 - 20
Breast	ACI rats with DES treatment [44]	0.43 MeV	X	100.
Lung	BALB/c mice [45]	Fission	γ	19
Breast	BALB/c mice [45]	Fission	γ	33
Lung*	RFM mice [46,47]	Fission	X or γ	22 - 55
Breast	RFM mice [46]	Fission	γ	17.

(* Existence of a threshold dose cannot be excluded.)

induction by neutrons in S-D rats have been fitted to a curve where response is proportional to $D_n^{0.5}$ [43]; however, the experimental data points do indicate high RBE values for very low doses (1 mGy) of fast neutrons whether or not this particular dose-response function is assumed to be correct. Breast cancer induction is highly influenced by hormone levels in the animal. In this respect, it is of considerable interest to note that high RBE values for low neutron doses could also be observed in ACI rats which received an implant of the female hormone diethylstilbestrol (DES) (Table 8), a treatment which in itself induces pituitary tumors and increases the susceptibility of the animals to radiation-induced breast cancers [44]. These values appear to remain unique in the field of tumor induction [7] and their relevance to radiation-induced breast cancer in humans remains uncertain.

Attempts have also been made to fit other data on cancer induction in mice to a curve in which response is proportional to $D_n^{0.5}$ [45]. The failure to find a linear relationship for neutron-induced cancers in animals has been interpreted as evidence that a multicellular reaction or a radiation-induced tissue factor is involved in cancer induction [48]. However, the data also fit a straight line in which response is directly proportional to D_n when corrections are made for increasing cell killing by increasing neutron doses [36]. This would imply a limiting value for the RBE of fast neutrons at low doses in these systems as well as for life shortening (see section B.5).

C. NEUTRON DOSIMETRY

The above section reviewed the biological data for the RBE for neutrons. Data such as that, along with LET considerations are usually sufficient to assign a quality factor, and hence calculate the dose equivalent, for most radiations. However, the calculation of dose equivalents for neutrons is much more complex.

In general, dose equivalent is calculated by the well known formula

$$H = QND$$

where H is the dose equivalent, Q the quality factor, N other modifying factors and D the absorbed dose. Currently, the ICRP recommends [4] that N be taken as unity for all radiations and that the quality factor be related to the collision stopping power (LET) of the radiation in water, as shown in Fig. 5. Thus, the dose equivalent can be calculated by calculating the absorbed dose in a small value element and multiplying it by the quality factor of the radiation that delivered the absorbed dose. If the quality factor for the radiation in question has a single value, such as for alpha particles, then the absorbed dose in a much larger volume, such as an organ, can be calculated and multiplied by Q to obtain the dose equivalent. However, neutrons do not have a unique value for Q, as neutron irradiation first results in the production of secondary heavy particles (such as protons and carbon, oxygen and nitrogen nuclei) and photons. The relative

contribution of heavy particles and photons to absorbed dose is energy dependent, as shown in Fig. 6 for neutrons normally incident on a 30 cm cylindrical phantom. It can be seen that secondary photons (Q = 1) contribute the most absorbed dose at 1 cm for neutron energies below 10 keV. In addition, since the neutron energy is rapidly moderated with depth in tissue, the relative contribution of photons to the absorbed dose increases with depth, which in turn results in the average quality factor for neutrons decreasing with depth in tissue. Fig. 7 illustrates this point.

The dose equivalents used in Fig. 7 are the results of calculations of the absorbed dose from each secondary heavy particle or phantom multiplied by its quality factor, and then summed over all particles contributing to the dose at any point. It can be seen that the ratio of dose equivalent to absorbed dose, which is taken as the quality factor for neutrons [50,51] varies with depth, and decreases rapidly for neutrons below 1 MeV. In this regard, it should be noted that the largest RBE values (Section B) were observed for neutron energies in the range of 0.5 MeV, and for small volumes, such as cells in a test tube, or mice. Those RBE values would considerably overestimate the risk from neutrons for neutron doses to organs within a human, as the neutron Q, and hence supposedly the RBE, is about a factor of five smaller at the midpoint of a 30 cm cylinder (taken to represent the trunk of a human) than at a depth of 1 cm.

Fig. 7 illustrates a major difficulty in assigning a quality factor of neutrons, as it varies considerably with depth and with energy. Attempts to address this issue by ICRU with the use of dose indices [52] and ambient dose equivalents [53] have not met with much success to date. The ICRP has addressed the issue [50] by defining an Effective Quality Factor, which is the ratio of dose equivalent to absorbed dose at the depth of the maximum dose equivalent. The dose equivalent as a function of depth for neutron energies are given in Fig. 8. Data such as that in Fig. 8 combined with that from Fig. 7 yield the effective quality factor as a function of neutron energy, as shown on Fig. 9. The curve labelled (b) on Fig. 9 was the quality factor recommended by ICRP [4,50] until its recent recommendation [1] to increase Q by a factor of 2.

The effective quality factor will overestimate the quality of the radiation that contributes to the dose to organs. Hence the use of the effective quality factor results in a conservative estimate of dose equivalent. In addition, it is common practise to assign the maximum dose equivalent [50, 51] or the dose equivalent at 1 cm [54] as the "whole body" dose equivalent from neutrons, which increases the conservatism in practical neutron dosimetry. The combined conservatism for 0.5 MeV neutrons, which is an approximate mean energy for leakage neutrons from reactors [eg. 55] can be as high as a factor of 1000 for tissue on the opposite side of a human body from the direction of the incident beam of neutrons (Fig. 8). However, in practise, neutrons can be incident on the body from all directions, and the average conservatism for most body organs would be about a factor of 10 for neutrons with energies in this region.

D. MICRODOSIMETRIC CONSIDERATIONS

It has been suggested [13,56,57] that microdosimetric quantities such as specific energy or lineal energy may be better measures of radiation quality than LET. These quantities have been used in theoretical models to aid in our understanding of reasons for the different shapes of dose response curves for different dose, dose rate and LET. One interpretation [13] of these models has been used to support a neutron RBE increasing with decreasing dose (i.e. as a function of $D^{-1/2}$). It seems reasonable therefore to review the basis for these models to see if they can be used as an aid in assigning a quality factor for neutrons.

The quantity specific energy (Z) is defined by

$$Z = \varepsilon/m$$

where ε is the energy deposited in a volume element with mass m. It should be noted that ε is a stochastic quantity, and can vary considerably about its mean value. Mean values of Z are usually expressed [58] as the frequency mean ($\bar{Z}_F$) or the dose mean ($\bar{Z}_D$). Z_F is the mean of the frequency distribution of specific energies for all volume elements having one and only one energy depositing event in it. $\bar{Z}_D$ is the mean of the dose distribution of specific energies for all volume elements having one and only one energy depositing event in it.

The quantity lineal energy (Y) is defined by

$$Y = \varepsilon / \bar{\ell}$$

where $\bar{\ell}$ is the mean chord length of the volume element. Mean values of Y can be expressed as the frequency mean or the dose mean as in the case of Z.

Fig. 10 gives the difference in the average specific energy in a 1 μm sphere for different quality radiations. At low doses the curves in Fig. 10 are horizontal. The reason for this is that the probability of more than one energy depositing event in any volume is small. Hence, the average specific energy in this region is $\bar{Z}_F$. As the dose increases, the probability of having more than one energy depositing event in a volume increases, and hence the average specific energy increases. At higher doses, the probability that there will be any volume without at least one energy depositing event is small, and in this region of dose the average specific energy is equal to the absorbed dose.

It is reasonable to assume that for doses below where the probability of having more than one energy depositing event per volume is small, the dose response curve will be linear. However, it should be noted that the specific energy per event may not be sufficient to induce some biological endpoints for low LET radiation, and in this case there would be no linear component to the dose response curve. Additionally, a particular biological endpoint may require damage to adjacent cells [13], and this would also result in there being no linear component for low LET radiation.

The relationship between absorbed dose and the probability that there will be more than one energy depositing events in a volume can be calculated using the Possion distribution. That is

$$P(x;\lambda) = \frac{e^{-\lambda}\,\lambda^{x}}{x!}$$

where x is the number of events and λ is the mean number of events. The probability of having more than one event is

$$P(x>1;\lambda) = 1 - e^{-\lambda}(1+\lambda)$$

and λ is the ratio of absorbed dose to Z_F. These probabilities are plotted as a function of dose in Fig. 11 for selected radiations.

It is unlikely that doses below those that result in a 2% probability of having more than one event in a volume would result in a dose response curve noticeably different from linear. Referring to Fig. 11, a linear dose response would be expected below about 2 Gy, 0.5 Gy, 0.08 Gy and 0.02 Gy for 0.6 MeV neutrons, 14 MeV neutrons, 200 kVp X-rays and Co-60 gamma rays respectively provided the critical biological target was about 1 μm in diameter. Non-linear dose response curves would be expected somewhat above these doses provided that the critical biological target was about 1 μm and that any cellular damage resulting from an event was not repaired before the second event occurred.

General dose response curves such as those in Fig. 1 can be explained using the above microdosimetric considerations. High LET radiations such as neutrons result in enough energy being deposited in a single event to cause the biological effect under consideration. Additional events in that volume before the cell has repaired itself either result in cell death, or if cell death is the endpoint, in "wasted" dose. The net result is for high LET radiation the dose response for acute radiation tends to be below that for chronic irradiation. Low LET radiation may not result in enough energy being deposited, on the average, in the critical volume to cause the biological effect being considered. It may be that only a small fraction of events (due to the stochastic nature of ε) have enough energy to cause the effect, and the dose response curve will be linear up to a dose where a second event is likely to occur, and the combined energy is enough to cause the biological effect. This will result in the acute dose response curve being above the chronic curve for low LET radiations, provided that the acute dose rate is sufficiently high that the second event occurs before the damage from the first is repaired.

An additional consideration to the effects of dose, dose rate and LET on the shape of the dose response curve is the size of the critical biological target, as this will have an effect on the specific energy as a function of dose (Fig. 10) and hence on the dose at which the probability of having more than one energy depositing event is significant. The approximate dependence

of the absorbed dose on the size of the critical biological target at which more than one event has a significant probability is given in Fig. 12 for 2 MeV neutrons.

The size of a critical biological target for the late stochastic effects of concern in radiation protection is unlikely to be greater than a few μm (cell nuclei are about 6-10 μm in diameter) and could easily be much less than one μm. Absorbed doses encountered in normal radiation practises are unlikely to greatly exceed 10^{-3} Gy per year for neutrons. Hence, microdosimetry would predict that dose response curves for occupational exposure to neutrons to be in the linear region (Region 2 of Fig. 12).

Similarly, absorbed doses for X-rays and gammas are unlikely to greatly exceed 10^{-2} Gy per year. Noting that the dose at which non-linearity will occur for these radiations varies with site diameter in a similar manner to that given in Fig. 12 [58], it is also likely that dose response curves for occupational exposures will also be linear for these radiations, as the horizontal region in Fig. 10 extends beyond 10^{-2} Gy.

The microdosimetric models described briefly above have had considerable success in explaining the observed differences in dose response curves with LET, dose, dose rate and biological endpoint. However, in order to use them to extrapolate measured values for the RBE of neutrons for a variety of biological endpoints in a diversity of species to the RBE for the induction of cancer or genetic effects in humans, one requires:

(1) Knowledge of the size of the critical biological target.

(2) The rate of repair of the damage to the cells in question.

(3) The possible effect of damage to adjacent cells in a complex biological organism.

Without this information, the extrapolation to effects in humans using microdosimetric theory is pure speculation.

E. DISCUSSION

The RBE values for induction of relevant biological endpoints by low doses of fast neutrons vary over a wide range (Tables 1-8). The recommended increase in the RBE of fast neutrons from 10 to 20 [1] may not seem unreasonable as a prudent measure on the basis of recent biological data such as those summarized in Tables 5 to 8, particularly if the RBE of ^{60}Co or ^{137}Cs γ-rays at low doses were never less than 0.8, as has been assumed by the ICRP [4]. This assumption is probably correct for high doses at high dose rate but is known to be incorrect at low doses for

induction of some biological endpoints where the effects of low doses of X-rays and γ-rays have been accurately measured (Tables 1, 2, 4 and 5). If the RBE of γ-rays were at low doses and/or low dose rates considerably less than that of 200 kVp X-rays for endpoints such as those given in Tables 6 and 8, the RBE values based on comparisons between fast neutrons and X-rays would look rather different. Unfortunately the required biological data for this comparison between γ-rays and X-rays at low doses and low dose rates are extremely limited or unavailable for these particular endpoints.

In another recent review of this topic, it was concluded that the average RBE for fission neutrons "is certainly higher than 10, and may well be of the order of 30-50 relative to gamma rays. A clear difference of about a factor of two between gamma rays and orthovoltage X rays is noted and should be recognized. Thus a ratio of 0.5:1:25 for gamma rays, orthovoltage X rays and fission neutrons would reasonably well represent the data" [49]. This conclusion appears to be supported by some of the data reviewed in Section B, but not all of it, in particular, Table 1 and Table 6.

In summary, there are serious problems associated with any proposed changes in Q to reflect these recent data on RBE of radiations of different quality.

(a) The biological data suggest that γ-rays are frequently 2 to 3 times less effective than X-rays at low doses and/or low dose rates. A corresponding decrease in Q for γ-rays would create major practical problems in the measurement of doses received by radiation workers.

(b) If Q for γ-rays were to be decreased by a factor of 2 to 3 to correspond more closely to recent RBE data, then crucial biological data on the RBE for radiation-induced translocations (Table 1), mutations and life shortening in mice (Table 6) would not support an increase in Q for fast neutrons.

(c) Most of the RBE values for fast neutrons have been determined using organisms of small physical dimensions. As noted in Section C, these values are not directly relevant to neutron doses received by internal organs in the human body, and this combined with the conservative practise of using the dose equivalent at 1 cm as whole body dose equivalent results in about a factor of 10 conservatism in practical neutron dosimetry around reactors.

F. CONCLUSION

This review of the scientific basis for the quality factor for neutrons does not indicate that there is any need for revision at this time. There are some experimental data that support an increase in the quality factor; however the relevance of these data to the occupational neutron exposures is uncertain.

It is recommended that no changes be made to the neutron quality factor, at least until the ICRP concludes its extensive review of the quality factor for all radiations.

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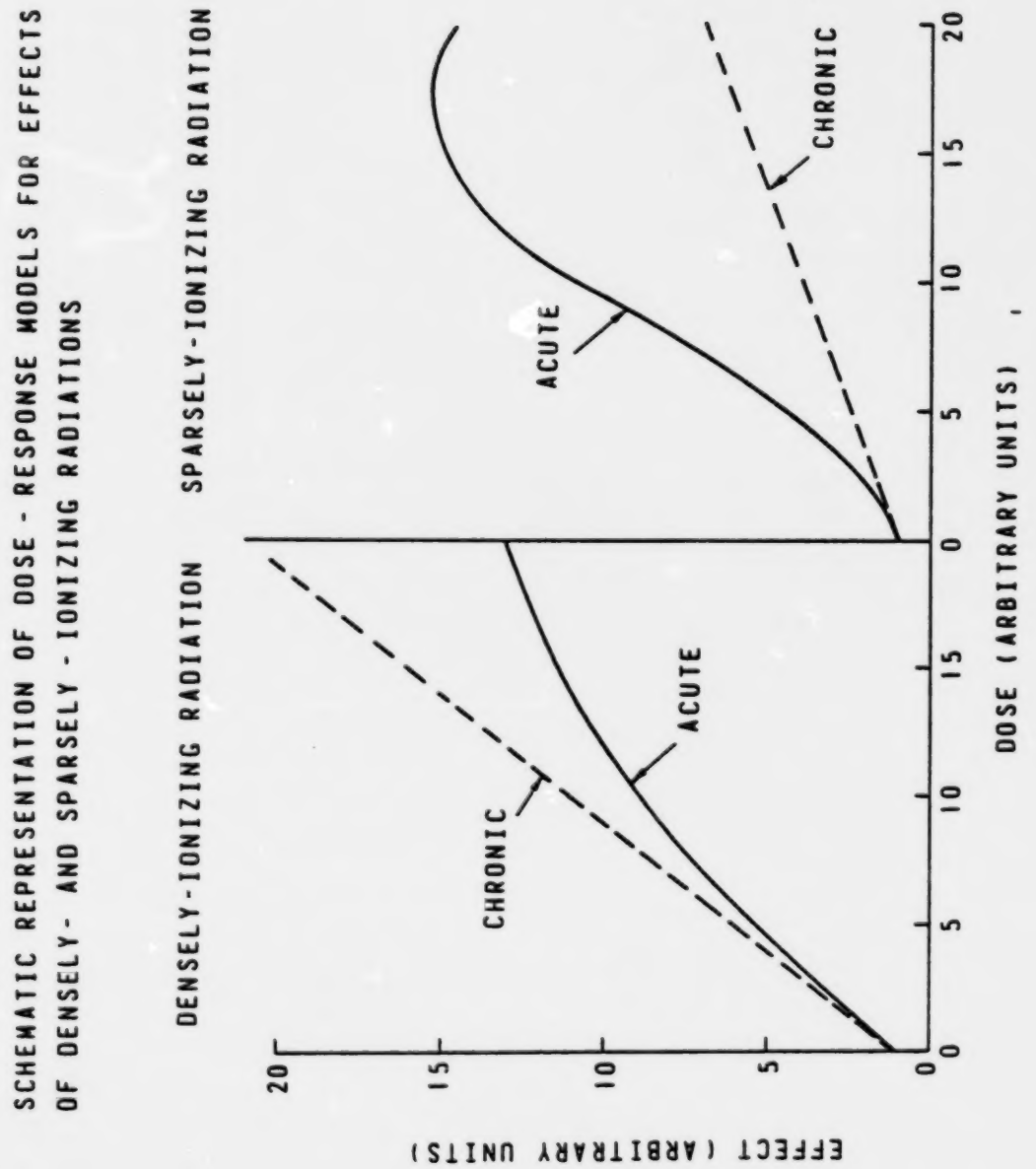

FIGURE 1 Schematic dose-response models for induction of biological changes by densely ionizing or high LET radiation (e.g. neutrons) and by sparsely ionizing or low LET radiation (e.g. X-rays). Solid lines: acute or high dose rate exposure. Dashed lines: chronic or low dose rate exposure.

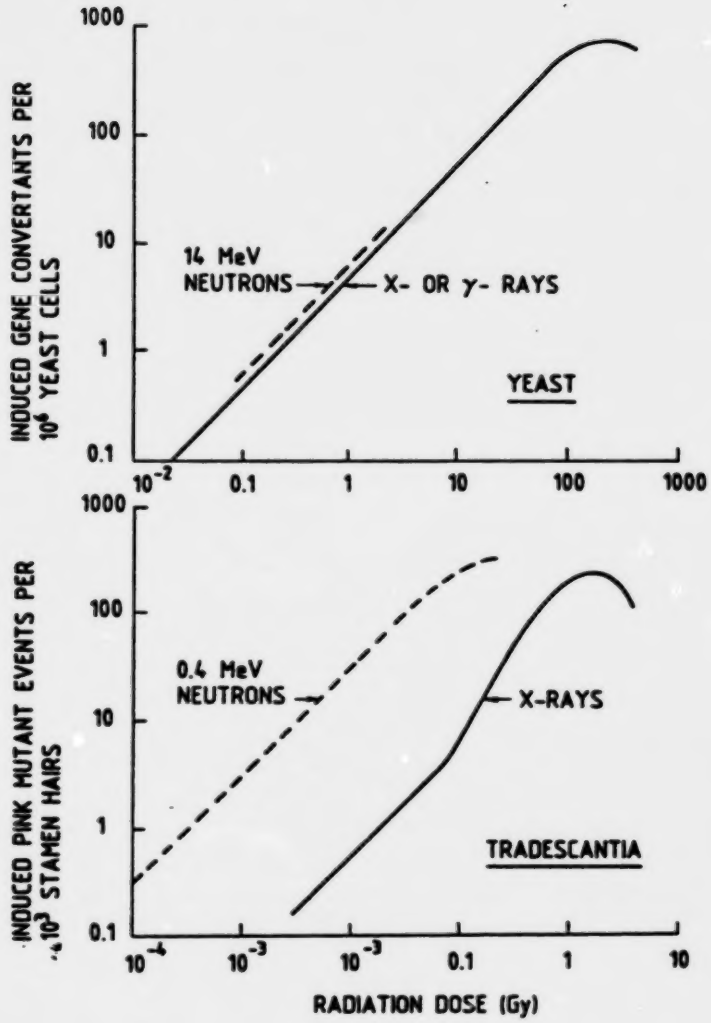

FIGURE 2 Dose-response curves for induction of gene conversion in yeast [25] and of pink stamen hair mutations in Tradescantia [26]. The doses and induced responses are both plotted on a logarithmic scale in order to portray data obtained over a very wide range of doses. In this plot, a slope of 1 represents a response which is directly proportional to dose; a slope of 2 represents a response which is proportional to dose squared. The experimental points (not shown) fall almost precisely on the lines shown.

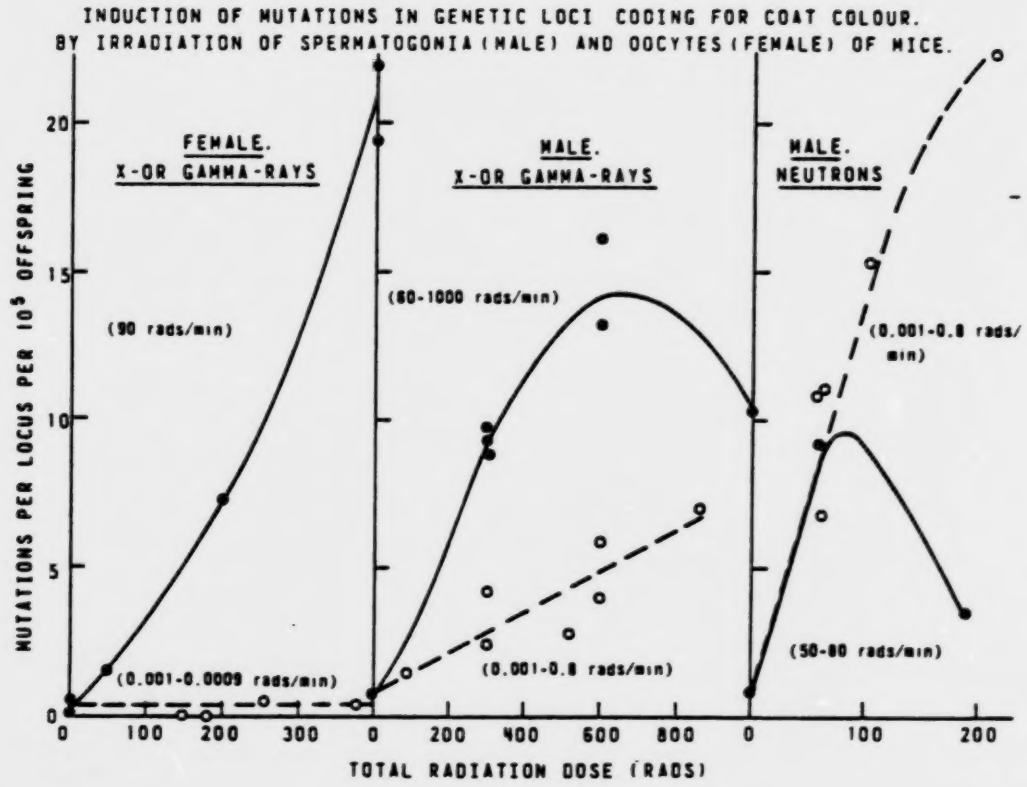

FIGURE 3 Dose-response curves for induction of coat-colour mutations following irradiation of spermatogonia in male mice or of oocytes in female mice. Data points are from Russell [17,30]; lines were drawn by eye. The low LET radiations used were X-rays for the high dose rates (solid lines) and gamma-rays for low dose rates (dashed lines); neutrons were 0.7 MeV. Note: 100 rad = 1 Gy.

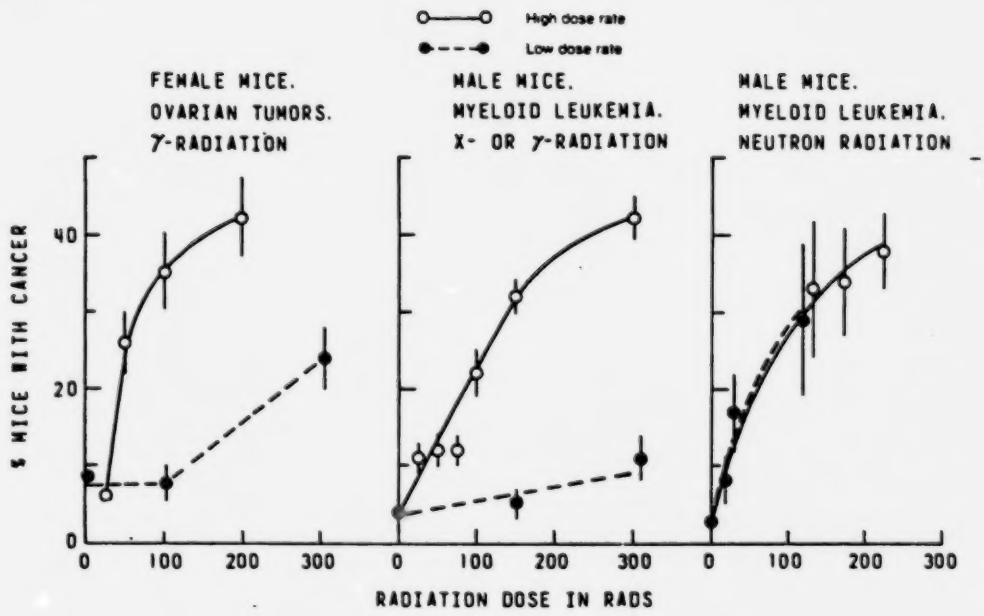

FIGURE 4 Dose-response curves for induction of two types of cancer in mice. Data points are from Upton et al [41]; lines were drawn by eye. Female mice were exposed to gamma-rays at 6.7 rad min^{-1} (solid line) or 0.0007-0.01 rad min^{-1} (dashed line). Male mice were exposed to X-rays at 80 rad min^{-1} (solid line) or to gamma-rays at 0.004-0.005 rad min^{-1} (dashed line). Dose rates for fission neutrons of about 0.7 MeV were 86 rad min^{-1} (solid line) or 0.0001-0.002 rad min^{-1} (dashed line). Note: 100 rad = 1 Gy.

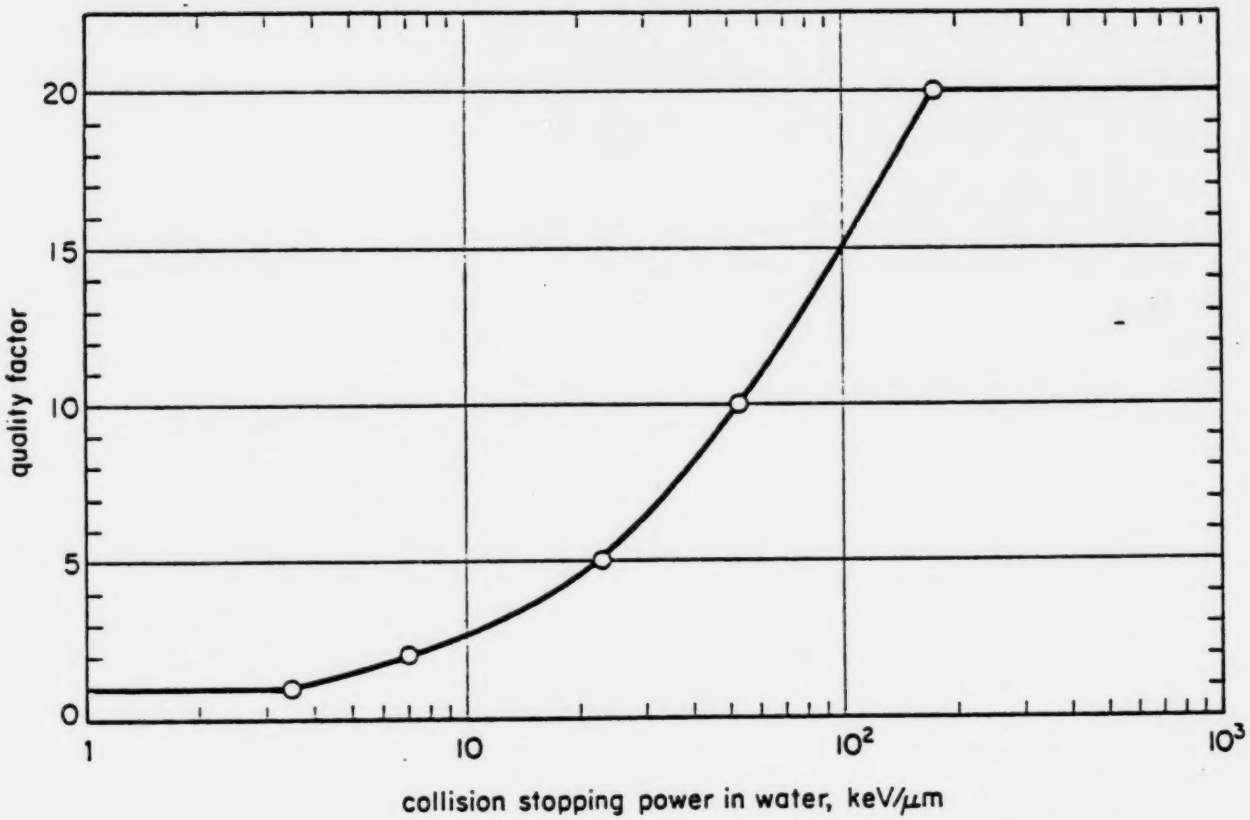

FIGURE 5 **The relationship between the collision stopping power in water (LET) and the quality factor recommended by the ICRP [50]. (Reproduced from reference 50.)**

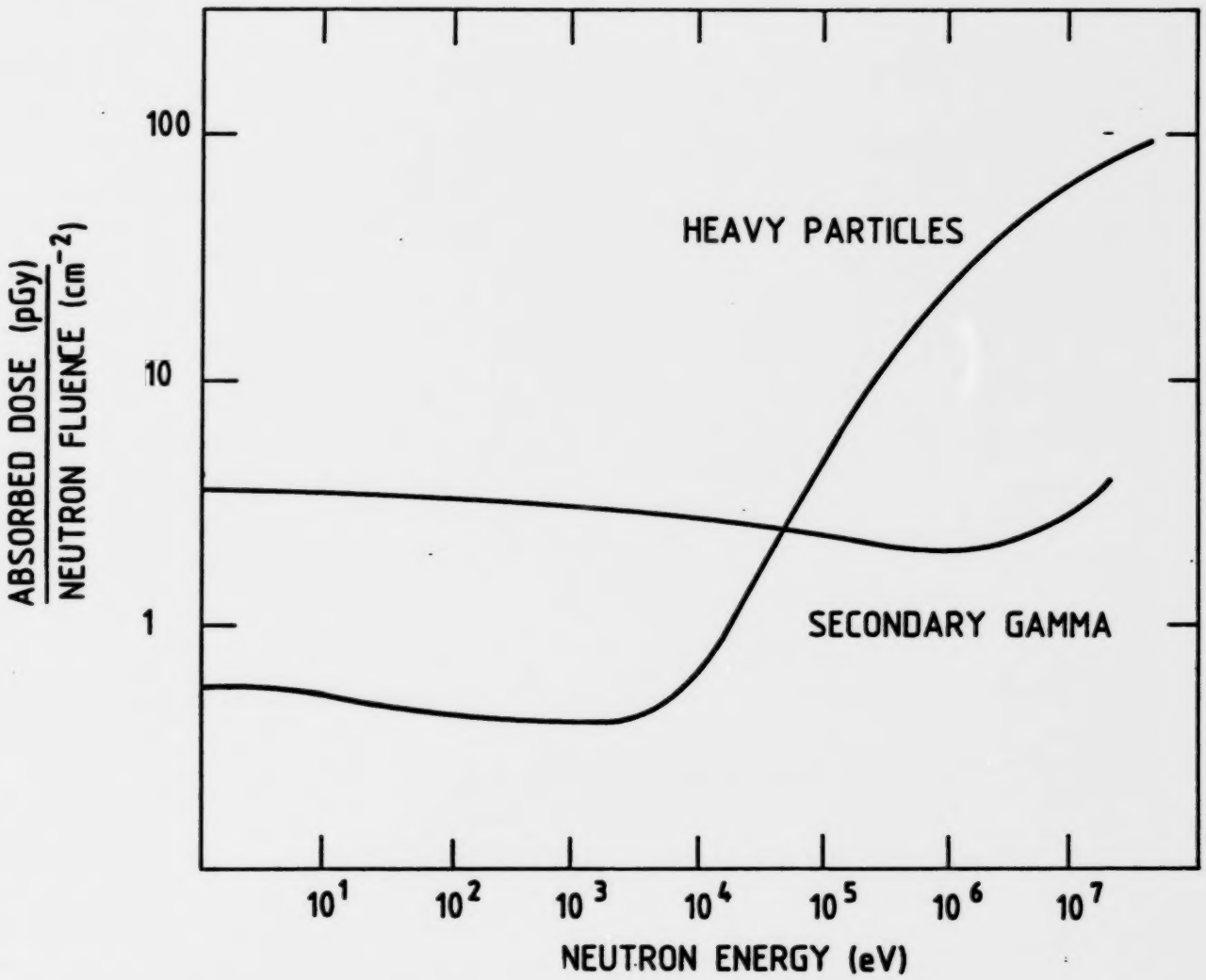

FIGURE 6 Contribution from heavy particles and secondary gammas to the absorbed dose at 1 cm depth in a 30 cm tissue equivalent cylinder for a neutron beam. (Data from reference 54.)

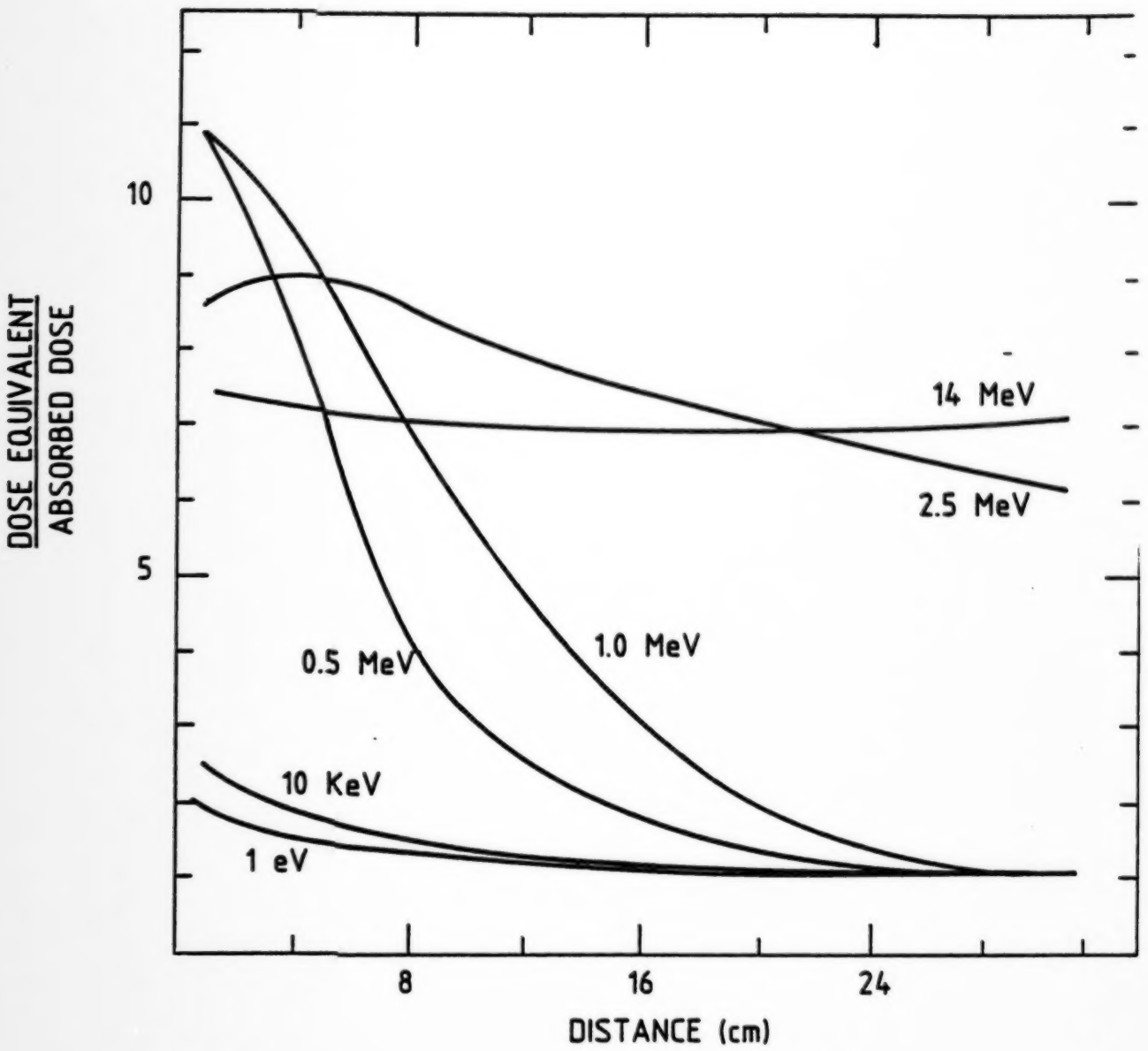

FIGURE 7 The ratio of dose equivalent to absorbed dose for selected neutron energies as a function of depth in a 30 cm diameter tissue equivalent cylinder. This ratio is taken to be the quality factor for neutrons. (Data from reference 51.)

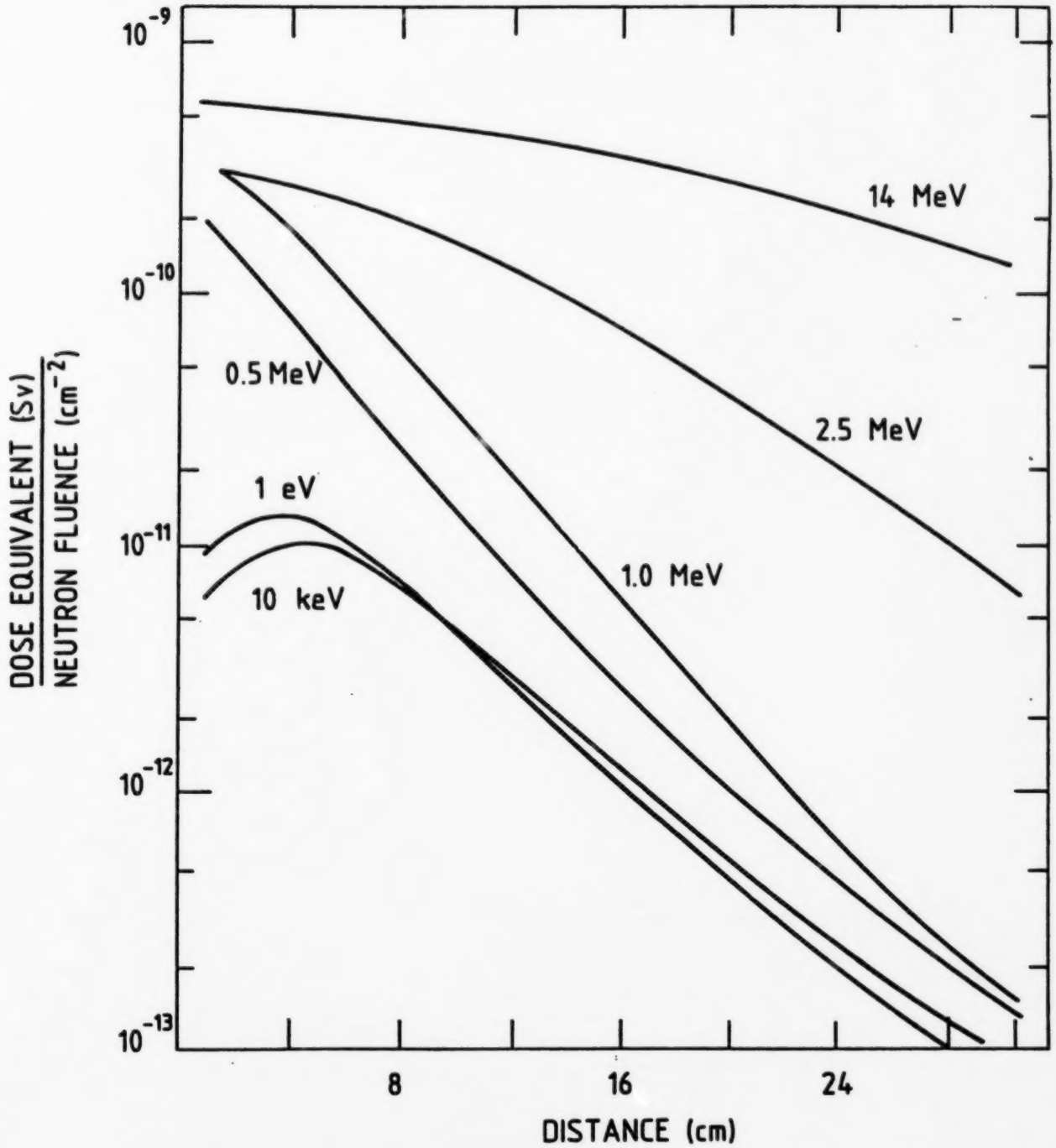

FIGURE 8 Dose equivalent as a function of depth in a 30 cm diameter tissue equivalent phantom for selected neutron energies. (Data from reference 51.)

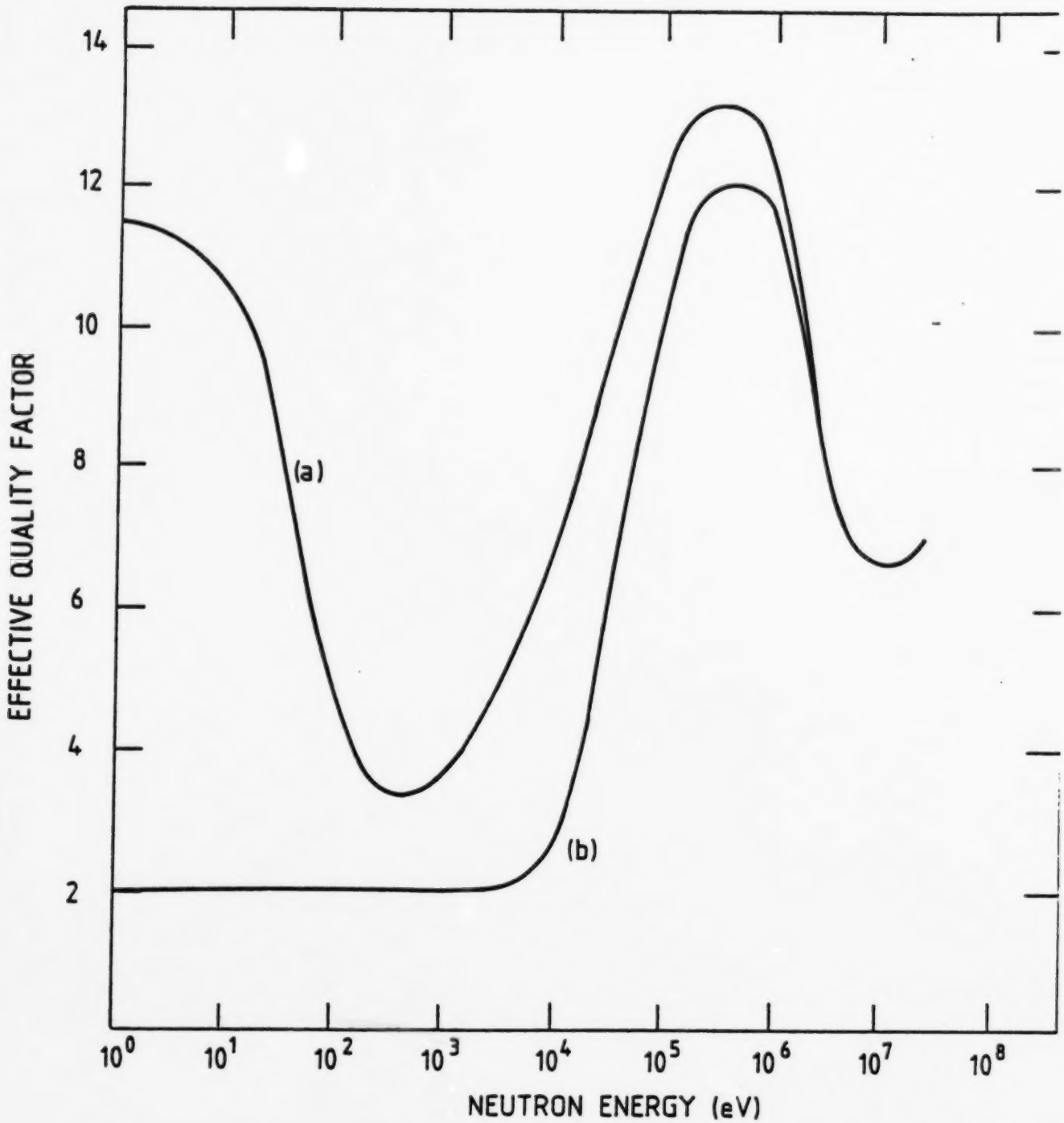

FIGURE 9 Effective quality factor (ratio of dose equivalent to absorbed dose at the point of maximum dose equivalent) for neutrons in a 30 cm diameter tissue equivalent cylinder (curve a) and in a small volume element (curve b). (Data taken from reference 51 and 54.)

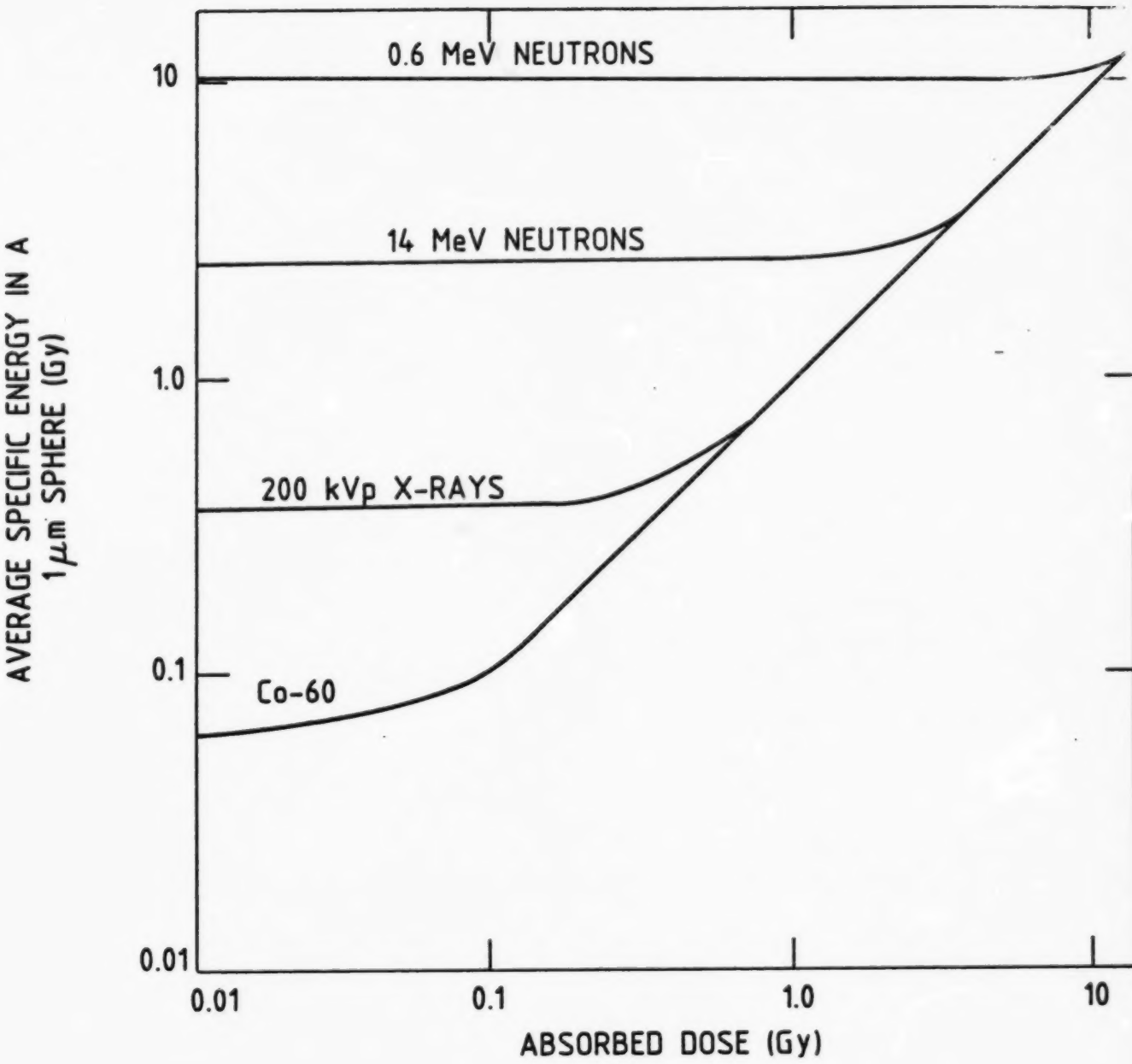

FIGURE 10 Average specific energy in a 1 μm tissue equivalent sphere as a function of absorbed dose for selected radiations.

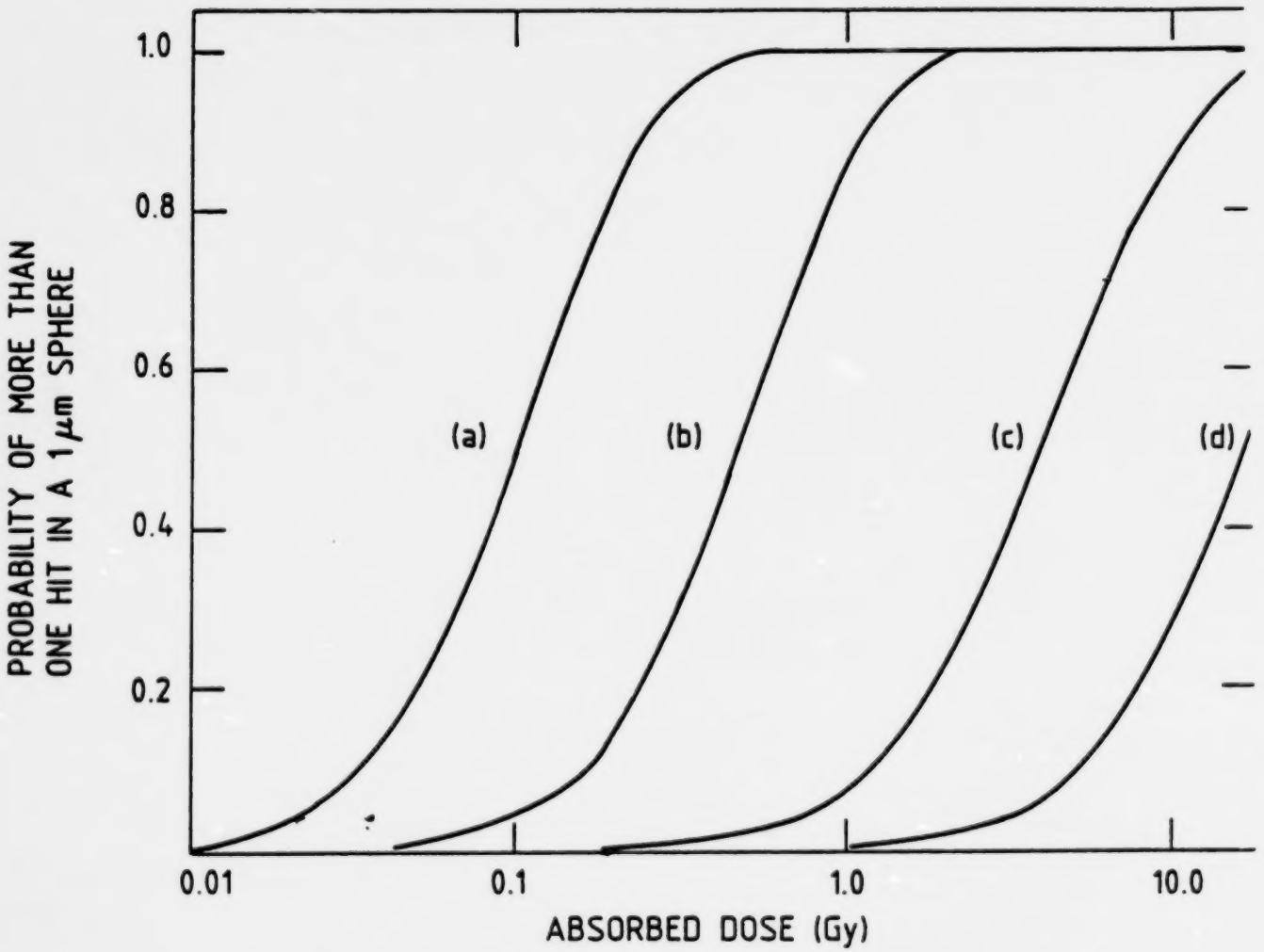

FIGURE 11 Probability of more than one hit (energy depositing event) in a 1 μm tissue equivalent sphere as a function of absorbed dose for selected radiations (a = Co-60, b = 200 kVp X-rays, c = 14 MeV neutrons and d = 0.6 MeV neutrons).

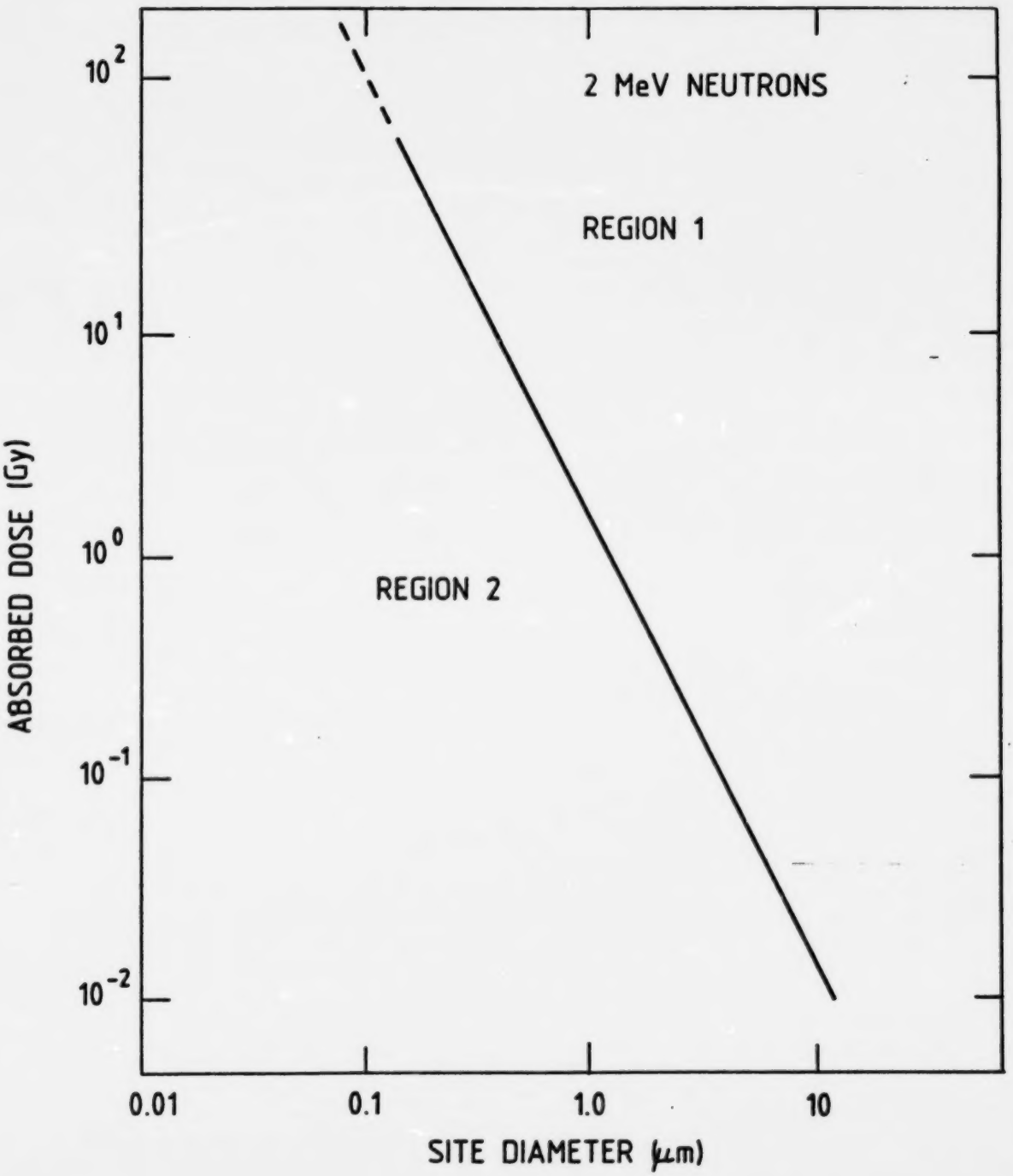

FIGURE 12 Absorbed dose to give a 2% probability that there will be more than one energy depositing event (hit) in a biological target (site) with the indicated diameter. Region 1 is for combinations of dose and size where the probability exceeds 2%, and region 2 is for combinations where it does not.